“STRESS HYPERGLYCEMIA”

an independent risk factor for

multivessel coronary artery disease in

Post myocardial infarction patients.

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CERTIFICATE

This is to certify that this dissertation entitled **"STRESS HYPERGLYCEMIA" an Independent risk factor for multi vessel coronary artery disease in post Myocardial infarction patients."** is a bonafide work done by Dr. B.Sasikumar, in partial fulfillment of regulations of the **Tamil Nadu Dr. M.G.R. Medical University, Chennai.**

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Declaration

I declare that this dissertation entitled "**STRESS HYPERGLYCEMIA" an independent risk factor for multi vessel coronary artery disease in post myocardial infarction patients** has been conducted by me under the guidance and supervision of **Prof. Dr. Paul. V. George M.D., D.M.** in the department of Cardiology Christian Medical College Vellore. It is submitted in partial fulfillment of the requirements for the award of the D.M. Cardiology, August 2008 examination to be held under Dr. M.G.R. Medical University, Chennai. This has not been submitted by me for the award of any degree or diploma from any other university.

Dr. B. Sasi kumar

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CONTENTS

Introduction:

Diabetes mellitus (DM) is an established major cardio vascular risk factor associated with increased prevalence of coronary artery disease. Patients with diabetes mellitus have higher incidence of acute myocardial infarction and congestive cardiac failure. Poor glycemic control and insulin resistance are associated with significant endothelial cell dysfunction, procoagulability and diffuse multi vessel disease. Individuals with diabetes mellitus who have acute myocardial infarction (AMI) have higher mortality than those without diabetes (1).

The significance of hyperglycemia observed after AMI has stimulated renewed interest. In recent years attention has been given to the evidence that the concomitant occurrence of hyperglycemia in patients admitted to intensive care units with an AMI enhance the risk of mortality and morbidity whether the patient has diabetes mellitus or not. Among patients with no prior history of diabetes, hyperglycemia may reflect previously diagnosed diabetes mellitus, preexisting carbohydrate intolerance, stress related carbohydrate intolerance, or a combination of these (2).

Glycometabolic state at hospital admission is an important risk marker for long term mortality in patients with AMI whether or not they have diabetes mellitus. Hyperglycemia occurring at admission in patients with suspected acute myocardial infarction generally represents stress hyperglycemia. The amount by which a patient's plasma glucose concentration increases during the early course of an AMI is determined by the levels of catecholamines and cortisol, which are in turn related to the infarct size, and degree of myocardial dysfunction (3, 4).

Abnormally elevated blood glucose is a common finding in patients with acute myocardial infarction

and has been referred to as stress hyperglycemia (SH). In a systematic overview and meta analysis, it was reported that SH was associated with an increased risk of mortality; the association was observed irrespective of the diabetic status of the patients, but was stronger in non diabetic patients. Moreover, the risk of congestive cardiac failure was also increased in non diabetic patients with SH (2).

Several large cohort studies indicate that an established relationship exists between plasma glucose levels at hospital admission and inhospital mortality in patients with AMI. Most of the studies done earlier examined the short term and long term prognosis associated with the hyperglycemia in AMI (8). However data regarding the relationship between stress hyperglycemia and the extent of coronary artery disease in non diabetic patients with AMI are limited. In this study we sought to determine the predictors and examine the association of SH during acute myocardial infarction and the extent of coronary artery disease especially the incidence of multivessel disease which is common in patients with diabetes mellitus.

Aim of the Study

High admission plasma glucose levels after acute myocardial infarction are common and associated with an increased risk of death in subjects with and without known diabetes mellitus. Recent data indicates a high prevalence of abnormal glucose metabolism with non-diabetic patients at the time of AMI.

We investigated the predictive value of stress hyperglycemia after AMI, for the extent of coronary artery disease(CAD) in patients with or without diabetes, particularly in those without preexisting diabetes but with impaired glucose tolerance during acute myocardial infarction and reverting to normal values after one month of post MI period.

Objectives:

1. To assess the incidence of stress hyperglycemia in patients with AMI in non-diabetic patients.
2. To compare the severity of coronary artery disease in patients, with stress hyperglycemia to those with normal glucose tolerance, and those known to have diabetes mellitus, in the setting of acute myocardial infarction.

Review of literature:

It is unclear whether stress hyperglycemia predisposes to worse outcome or is simply a marker of poor prognosis (5). Though inconclusive, studies suggest that stress hyperglycemia may be a marker of extensive myocardial damage. Better established through in-vitro studies is the fact that an elevated blood glucose level, whether acute or chronic, adversely affects endothelium-dependent vasodilatation and impairs macrophage and lymphocyte function(5).

Up to half of the patients with acute myocardial infarction have been recognized as having raised blood glucose concentration. Hyperglycemia occurring at admission in patients with suspected AMI generally represents stress hyperglycemia. In recent years, much attention has been given to the evidence that the concomitant occurrence of hyperglycemia in patients admitted to intensive care units with an acute myocardial infarction enhances the risk of mortality and morbidity, whether the patient has diabetes or not.(5)

In some cases, the elevation of glucose could simply be a marker of pre-existing, but not yet detected, type 2 diabetes or impaired glucose tolerance. Besides being causal, elevated glucose could also be a marker of existing insulin resistance and or beta cell failure that may contribute to the poor prognosis through other mechanisms. Consequently, the prevalence of stress hyperglycemia, understanding the possible mechanisms through which hyperglycemia worsens the prognosis of MI, as well the effectiveness of its control during acute MI, seems to be of great relevance.(9)

Stress hyperglycemia and pathogenesis:

High blood glucose levels after AMI may be the result of high levels of circulating stress hormones; these may also be an indicator of incipient pancreatic Beta cell failure that becomes unmasked under stressful condition and existing insulin resistance. Oswald in their study has stated that concentration of cortisol, and adrenaline are the main determinants of measured plasma glucose concentration. (3)

According to Nazneem, hyperglycemia during AMI may reflect a compromised metabolic state and is associated with a surge of serum catecholamines and decreased insulin sensitivity that increases the turnover of potentially harmful free fatty acids(4).

J. Sala et al in their study has found that the plasma non adrenaline and cortisol concentrations increase in the acute phase of MI and trigger a non specific stress reaction leading to an impaired plasma insulin response resulting in hyperglycemia (10).

C Weston has pointed out that hyperglycemia is an epiphenomenon a marker of large infarcts and poor left ventricular function resulting from catecholamine induced change in glucose metabolism rather than a reflection of insulin resistance (11).

Timmer in his study has stated that hyperglycemia is accompanied by high levels of catecholamines such as cortisol , adrenaline, increased glycogenolysis and lipolysis and decreased insulin sensitivity. Glucose abnormalities are very common in patients with AMI but without previously known type II diabetes (12).

M Wallender in his study has pointed out that glucose abnormalities seems to be related to impaired beta cell function and implies that dysglycaemia immediately after an infarction is not a stress epiphenomenon but reflects stable disturbances of glucose regulation proceeding the AMI(13).

Antonio Ceriello et al have also quoted that elevation of glucose could simply be a marker of preexisting but not yet detected type 2 diabetes or impaired glucose tolerance. It could also be a marker of existing insulin resistance or beta cell failure that may contribute to poor prognosis through other mechanism (14).

According to Husband DJ, there is no evidence, that stress hyperglycemia during acute MI is an indicator of preexisting diabetes. He also proposed that admission blood glucose greater than or equal to 10mmol/L in patients with MI is more likely to indicate previously undiagnosed diabetes than stress hyperglycemia. There is no evidence that myocardial infarction precipitates diabetes. The glycosylated haemoglobin concentration (HA1c) can be used to distinguish between stress hyperglycemia and hyperglycemia caused by diabetes (9).

Masaharu Ishihara et al in their study stated that admission hyperglycemia in non diabetic patients with AMI does not represent previously undiagnosed abnormal glucose tolerance. Fasting glucose and HbA1c rather than admission glucose may be useful to predict abnormal glucose tolerance and they finally concluded in their studies that OGTT should be considered in all non diabetic patients with AMI (15).

Utility of HbA_{1c} Levels for Diabetes Case Finding in Hospitalized Patients with Hyperglycemia

Patients presenting to the hospital with an acute illness and found to be hyperglycemic on admission can have either stress-related hyperglycemia or unrecognized impairment of glucose tolerance, including frank diabetes. A sizable proportion of this population will truly have diabetes; with prevalence estimates from 7 to 63%.There is at present no quick and accurate method for distinguishing between these two conditions (16).

The oral glucose tolerance test (OGTT) is impractical because of dietary and cost constraints, it is less convenient and acceptable to patients, and it may even be contraindicated in acutely ill patients. The fasting plasma glucose (PG) test, on the hand, would require the coordination of at least two morning fasting levels. HbA_{1c} level is considered an important monitoring tool in treating patients with diabetes, but it is not currently recommended for screening or for the diagnosis of diabetes. HbA_{1c} level reflects the average plasma glucose to which the hemoglobin is exposed during the erythrocyte's life span of ~ 90 days and may be less influenced by the acute stress of illness(16).

Although the utility of HbA_{1c} levels for diagnosis and screening of diabetes has been studied in the general population, its role in differentiating patients with true diabetes from those with random stress-induced hyperglycemia in the hospital has not been previously investigated (16).

The use of the HbA_{1c} level can play a major role in diabetes case finding in hospitalized patients with random hyperglycemia, where the operating characteristics of the test approach those of the traditional fasting plasma glucose for the diagnosis of diabetes. An admission HbA_{1c} level is a quick and convenient tool for the diagnosis of diabetes and, in ~50% of the cases, could eliminate the need for further diagnostic testing (through fasting plasma glucose or oral glucose tolerance test determinations). This quicker diagnosis of diabetes with the HbA_{1c} level can also translate into an early inpatient mobilization of diabetes support services (e.g., nutrition and education), treatment, and even

early medication response (16).

Hyperglycemia and acute cardio vascular effects:

Hyperglycemia independently of diabetic status is a well known predictor of cardiovascular disease and its progression, resulting in increased mortality.

Acute cardio vascular effects (Stuart) (17):

1. Endothelial dysfunction.

2. Platelet hyper reactivity.

3. Increased cytokine activation.

4. Increased lipolysis and free fatty acid.

5. Reduced glycogenolysis and glucose oxidation.

6. Increased oxidative stress.

7. Impaired micro circulatory function.

8. Impaired ischaemic preconditioning

9. Impaired insulin secretion and insulin stimulated glucose uptake.

Toxic effects of hyperglycemia on cell function.

Sala in their study has quoted that acute hyperglycemia induces oxidative stress probably via generation of free radicals (10). This may occur by auto oxidation of glucose, labile glycation or intra cellular activation of the polyol pathway. Increased glucose level can also increase protein kinase C activity. For example increased endothelin secretion and also increased expression of adhesion molecules on the vascular endothelium involved in macrophage activation.

Stuart has also stated that the degree of oxidative stress correlates most closely with acute not chronic glucose fluctuations. Both direct and indirect evidence supports this concept. Indirect evidence is obtained through the use of antioxidants. The fact that antioxidants can hinder some of the effects acutely induced by hyperglycemia, endothelial dysfunction, activation of coagulation, and inflammation, suggests that the action of acute hyperglycemia is mediated by the production of free radicals (17).

Direct evidence is linked to the estimate of the effects of acute hyperglycemia on oxidative stress markers. It has been reported that during oral glucose challenge, a reduction in the antioxidant defenses, and an increase in markers of oxidative stress is observed (19).

Effects of stress hyperglycemia on endothelium:

Endothelial dysfunction plays a key role in cardiovascular disease. Endothelial dysfunction is a common feature after an MI. Stuart has stated that acute hyperglycemia rapidly suppress flow mediated

vasodilatation through increased production of O2 derived free radicals. Hyperglycemia increases the expression of tissue factor, and plasminogen activation inhibitor I through activation of inflammatory transcription factor. J Sala has stated that acute hyperglycemia produces vasoconstriction through nitric oxide reduction which is mediated by free radicals (10).

One proposed link between hyperglycemia and poor cardiovascular outcomes is the effect of acute hyperglycemia on the vascular endothelium. In addition to serving as a barrier between blood and tissues, vascular endothelial cells play a critical role in overall homeostasis. In the healthy state, the vascular endothelium maintains the vasculature in a quiescent, relaxant, antithrombotic, antioxidant, and antiadhesive state. During illness the vascular endothelium is subject to dysregulation, dysfunction, insufficiency, and failure (18)

Endothelial cell dysfunction is linked to increased cellular adhesion, perturbed angiogenesis, increased cell permeability, inflammation, and thrombosis. Commonly, endothelial function is evaluated by measuring endothelial-dependent vasodilatation, looking most often at the brachial artery. Human in vivo studies utilizing this parameter confirm that acute hyperglycemia to the levels commonly seen in the hospital setting (142–300 mg/dl or 7.9–16.7 mmol/l) causes endothelial dysfunction (18)

Hyperglycemia may directly alter endothelial cell function by promoting chemical inactivation of nitric oxide Other mechanisms include triggering production of reactive oxygen species (ROS) or activating other pathways (rev. Despite compelling experimental data, studies examining a possible association among hyperglycemia, endothelial function, and outcomes have not to date been done in hospitalized patients (18).

Stress Hyperglycemia and thrombosis:

Antonio Ceriello et al in their study has stated that acute hyperglycemia induces a shortening of the fibrinogen half life and increases in fibrino peptide A, fragments of pro-thrombin, in factor VII and in platelet aggregation suggesting an increased activation of thrombosis (14).

Sala has also stated that increased plasminogen activator inhibitior I and decreased fibrinolytic activity increases the thrombogenicity. Katsuomi also says that hyperglycemia augments thrombus formation (10).

Timmer et al has pointed out that hyperglycemia increases inflammatory response. Systemic inflammation is a potent prothrombotic stimulus, promoting procoagulant factors, inhibiting natural anticoagulants and increasing platelet activation. These may explain the prothrombotic properties associated with hyperglycemia (12).

Gresele et al. showed that acute hyperglycemia increases platelet activation in diabetic patients as well as in patients with stress hyperglycemia in non diabetics Further more, recent evidence showed that acute hyperglycemia increases inflammatory responses during STEMI. These elevations of inflammatory responses in hyperglycemic subjects with STEMI may partly explain the poor response to lysis(14).

Multiple studies have identified a variety of hyperglycemia-related abnormalities in hemostasis, favoring thrombosis. For example, hyperglycemic changes in rats rapidly reduce plasma fibrinolytic activity and tissue plasminogen activator activity while increasing plasminogen activator inhibitor (PAI)-1 activity (18).

Human studies in patients with type 2 diabetes have shown platelet hyperactivity indicated by increased thromboxane biosynthesis. Thromboxane biosynthesis decreases with reduction in blood glucose. Hyperglycemia-induced elevations of interleukin (IL)-6 levels have been linked to elevated plasma fibrinogen concentrations and fibrinogen mRNA. Increased platelet activation as shown by shear-induced platelet adhesion and aggregation on extracellular matrix has been demonstrated in patients with diabetes (18).

As little as 4 hours of acute hyperglycemia enhances platelet activation in patients with type 2 diabetes. In a crossover, double-blind study, 12 patients were subjected to hyperglycemic (250 mg/dl, 13.9 mmol/l) and euglycemic (100 mg/dl, 5.55 mmol/l) clamps. Hyperglycemia precipitated stress-induced platelet activation as well as platelet P-selectin and lysosomal integral membrane protein (LIMP) expression. Hyperglycemia also caused increased plasma von Willebrand factor antigen, von Willebrand factor activity and urinary 11-dehydro-thromboxane B_2 (a measure of thromboxane A_2 production). These changes were not seen in the euglycemic state. If hyperglycemia-induced platelet hyperreactivity is particularly evident with high–shear stress conditions, as suggested in the above studies, this finding may explain the increased thrombotic events commonly seen in hospitalized patients with diabetes (18).

Stress hyperglycemia and Impaired insulin secretion:

Capes et al has pointed out that hyperglycemia is a reflection of relative insulin deficiency which is associated with increased lipolysis and excess circulating free fatty acids. Free fatty acids are toxic to ischemic myocardium and may lead to damaged cardiac cell membrane, calcium overload and arrhythmias. High concentrations of free fatty acids during myocardial ischaemia increase myocardial

oxygen demand and reduce myocardial contractility (2).

Iwan et al in their article has pointed out that relative insulin deficiency decreases glucose transporter translocation to the cell surface and increases free fatty acids through increased lipolysis in adipose tissue. Glucose utilization is reduced and free fatty acids are mainly used in the myocardium. This results in increased oxygen demand and in ischemic myocardium, accumulation of unoxidized products of free fatty acids. Free fatty acids inhibit glucose oxidation to a greater extent than glucose uptake (20).

Stuart also stated that acute hyperglycemia is a reflection of relative insulinopenia which is associated with increased lipolysis and free fatty acid generation as well as diminished myocardial glucose uptake (17).

These findings indicate that impaired glucose tolerance plays a pathological role and its diagnosis based on oral glucose tolerance test is important in patients with coronary artery diseases.

Stress Hyperglycemia and no-reflow phenomenon:

Katsuomi has explained the association between hyperglycemia and the no-reflow phenomenon. Large infarct is more likely to cause catecholamine release which affects fatty acid and glucose homeostasis. Acute hyperglycemia also increases intercellular adhesion molecule1 level or P selectin which augments plugging of leukocytes in the capillaries. Leucocytes trapped in the coronary capillaries and venules might further contribute to the no reflow phenomenon (21).

Stuart had showed that acute hyperglycemia is associated with reduced TIMI grade 3 flow and is the

most important predictor of absence of coronary perfusion. He also states that acute hyperglycemia is associated with impaired microcirculatory function as manifest by no reflow myocardial contrast echocardiography after percutaneous coronary intervention (PCI) (17).

Ishihara et al in their study stated that acute hyperglycemia but not diabetes is a predictor for inhospital mortality after AMI in the PCI era (22). No reflow occurred more frequently during PCI in patients with acute hyperglycemia, suggesting that microvascular dysfunction might have contributed to adverse outcome of these patients.

Timmer et al in their study quoted that hyperglycemia in patients with STEMI is an important predictor of impaired epicardial flow before reperfusion therapy and also stated that further investigation to improve coronary flow of the infarct related artery before reperfusion is warranted in hyperglycemic patients (12).

Stress hyperglycemia - Role of inflammatory immune process:

Raffacle et al in their study investigated 108 patients with acute MI. He found that 31 new hyperglycemic patients had higher infarct segment length and myocardial performance index and reduced trans mitral Doppler flow, pulmonary flow and ejection fraction compared with 36 hyperglycaemic diabetic patients and 41 normoglycemic patients(23).

Hyperglycaemic patients have higher circulating level of IL- 18 and CRP. Both are strong predictors of death from cardiovascular causes in patients with acute coronary syndrome. Hyperglycaemia is also associated with enhanced T cell activation the immune system has developed mechanism to limit the

immune process including enhanced expression of CD 152 which has a negative regulatory function in T cell activation(23).

There is impaired expression of CD 152 in hyperglycaemic patients. High glucose may also interfere with autoregulatory function of T cell activation which maybe implicated in the prolongation of the inflammatory process and poor cardiac outcome (23).

Marfella et al in their study stated the association between inflammatory immune markers and functional cardiac outcome in patients with a first uncomplicated MI. Stress hyperglycemia was found to be associated with amplified inflammatory immune reactions and worse functional cardiac outcome (23).

Hyperglycemia and immune function

The association of hyperglycemia and infection has long been recognized, although the overall magnitude of the problem is still somewhat unclear. From a mechanistic point of view, the primary problem has been identified as phagocyte dysfunction. Studies have reported diverse defects in neutrophil and monocyte function, including adherence, chemotaxis, phagocytosis, bacterial killing, and respiratory burst (18).

Bagdade et al. were among the first to attach a glucose value to improvement in granulocyte function when they demonstrated significant improvement in granulocyte adherence as the mean fasting blood glucose was reduced from 293 ± 20 to 198 ± 29 mg/dl (16.3–11 mmol/l) in 10 poorly controlled patients with diabetes. Other investigators have demonstrated similar improvements in leukocyte function with treatment of hyperglycemia. In vitro trials attempting to define hyperglycemic thresholds

found only rough estimates that a mean glucose >200 mg/dl (11.1 mmol/l) causes leukocyte dysfunction (22)

Alexiewicz et al. demonstrated elevated basal levels of cytosolic calcium in the polymorphonuclear leukocytes (PMNs) of patients with type 2 diabetes relative to control subjects. Elevated cytosolic calcium was associated with reduced ATP content and impaired phagocytosis. There was a direct correlation between PMN cytosolic calcium and fasting serum glucose. These were both inversely proportional to phagocytic activity. Glucose reduction with glyburide resulted in reduced cytosolic calcium, increased ATP content, and improved phagocytosis. Classic microvascular complications of diabetes are caused by alterations in the aldose reductase pathway, advanced glycated end products (AGE) pathway, reactive oxygen species pathway, and the protein kinase C (PKC) pathway. Several of these pathways may contribute to immune dysfunction. PKC may mediate the effect of hyperglycemia on neutrophil dysfunction (23).

Liu et al. found that decreased phagocytic activity in diabetic mice correlated inversely with the formation of advanced glycation end products, although a direct cause-and-effect relationship was not proven (24).

Ortmeyer and Mohsenin found that hyperglycemia caused impaired superoxide formation along with suppressed activation of phospholipase D. Reduced superoxide formation has been linked to leukocyte dysfunction. Another recent study found a link among hyperglycemia, inhibition of glucose-6-phosphate dehydrogenase, and reduced superoxide production in isolated human neutrophils (25)

Sato and colleagues used chemiluminescence's to evaluate neutrophil bactericidal function. The authors confirmed a relationship between hyperglycemia and reduced superoxide formation in

neutrophils. This defect was improved after treatment with an aldose reductase inhibitor. This finding suggests that increased activity of the aldose reductase pathway makes a significant contribution to the incidence of diabetes-related bacterial infections. Laboratory evidence of the effect of hyperglycemia on the immune system goes beyond the granulocyte. Nonenzymatic glycation of immunoglobulin has been reported. Normal individuals exposed to transient glucose elevation show rapid reduction in lymphocytes, including all lymphocyte subsets (28).

In patients with diabetes, hyperglycemia is similarly associated with reduced T-cell populations for both CD-4 and CD-8 subsets. These abnormalities are reversed when glucose is lowered. In summary, studies evaluating the effect of hyperglycemia on the immune system comprise small groups of normal individuals, patients with diabetes of various duration and types, and animal studies. These studies consistently show that hyperglycemia causes immunosuppression. Reduction of glucose by a variety of means reverses the immune function defects (18).

Stress hyperglycemia and impaired ischemic preconditioning:

Ischemic preconditioning powerfully limits myocardial infarct size in vivo and plays an important role to reduce the extent of myocardial infarction. Hyperglycemia alters the protection afforded by ischemic precondition. It impairs ATP sensitive K channel an important mediator of ischemic preconditioning (21).

Activation of Potassium ATP channel is potentiated by nitric oxide and acute hyperglycemia has been shown to impair nitric oxide availability and shortening of action potential duration which contribute to the cardio protective effects of ischemic preconditioning. Aute hyperglycemia prolongs action

potential duration and slows intra cellular calcium clearing. Hyperglycemia abolishes reduction of myocardial infarct size afforded by ischemic preconditioning (21).

Katsuomi has also pointed out that acute hyperglycemia is known to abolish the effect of ischemic preconditioning probably through attenuation of mitochondrial adenosine triphosphate which regulates potassium channel activation. It also reduces collateral flow to the area at risk resulting in greater myocardial damage before reperfusion (21).

Hyperglycemia and coronary artery disease:

Patients with diabetes and stress hyperglycemia had advanced disease on presentation and much higher mortality than those with normal blood glucose. The mortality difference is the result of more advanced disease rather than hyperglycemia.

Christopher et al evaluated base line morning blood glucose concentration with respect to subsequent coronary disease from 24,160 non diabetic patients (29). The study demonstrated that elevated glucose in the absence of diabetes is associated with other recognised risk factors including age, weight, hyperlipidemia, renal failure and hypertension. Pathologic consequences associated with elevated blood glucose may be related to both glucose concentration and insulin. Vascular disease may be related to endothelial dysfunction, proinflammatory changes and a prothrombotic state. Elevated glucose induces non enzymatic protein glycosylation, protein kinase C activation and oxidative stress.

Capes et al has stated that patients who develop stress hyperglycemia are likely to be dysglycaemic when not stressed. Patients with dysglycaemia (who have blood glucose concentration higher than the

normal range but lower than the threshold for diabetes.) are at a higher rate of cardio vascular disease than patients who have normal glucose and may have a worse prognosis after AMI because of more extensive coronary artery disease(2)

Yu Kataoka et al investigated the morphological characteristics of coronary arteries in patients with impaired glucose tolerance using computer assisted coronary angiography. A total of 534 patients with angina pectoris were studied. He concludes that impaired glucose tolerance is associated with diffuse small vessel narrowing (31).

Stress hyperglycemia and arrhythmias:

In MI, an increased plasma glucose level has been demonstrated to be capable of inducing such electrophysiological alterations as to favour the occurrence of arrhythmias, whose outcome could be fatal.

Marfella et al in their study stated that an acute increase of glycaemia in normal subjects produces a significant QT prolongation, and confirmed by in an vitro model of working heart from rat by D'amico et al in their study(23).

Hyperglycemia and coagulation defects:

It has been reported that increased platelet activation after an MI is correlated with hyperglycaemia in non-diabetic patients. The possible role of hyperglycemia in the activation of blood coagulation has previously been reviewed. It emerges that acute glycaemic variations are matched with a series of

alterations in coagulation that are likely to cause thrombosis. Acute hyperglycemia induces a shortening of the fibrinogen half life, and increases in firbinopeptide A, fragements of prothrombin, infactor VII, and in platelet aggregation, which are all phenomena suggesting increased activation of thrombosis(23)

Stress hyperglycemia and LV remodeling:

Marcus et al. has stated that hyperglycemia may promote an osmotic diuresis, leading to a reduced circulating volume and decreased end-diastolic and stroke volume through interference with the Frank-starling mechanism of myocardial contractility.

Christophe et al analyzed LV remodeling in 162 non-diabetic patients with anterior MI. systematic echocardiographic follow up was performed at 3 months and 1 year after MI. The changes in EDV and ESV were recorded. LV remodeling defined as more than 20% increase in EDV and was observed in 46% patients in the stress hyperglycemia group (32).

Stress hyperglycemia remained a major predictor of LV remodeling. At least two possible explanations may account for this observation. Stress hyperglycemia on admission can either be an indicator of concomitant metabolic abnormalities which may themselves play a role in the remodeling process (higher free fatty acid concentration, insulin resistance and impaired myocardial glucose use) or alternatively can simply be a marker of more extensive myocardial damage (32).

Potential relationships between metabolic stress hyperglycemia, hypoinsulinemia, and poor hospital outcomes

To explain the dual role of glucose and insulin on hospital outcomes, Levetan and Magee proposed the following relationships. Elevations in counter regularory hormones accelerate catabolism, hepatic gluconeogenesis, and lipolysis. These events elevate blood glucose, free fatty acids, ketones, and lactate. The rise in glucose blunts insulin secretion via the mechanism of glucose toxicity, resulting in further hyperglycemia (27).

The vicious cycle of stress-induced hyperglycemia and hypoinsulinemia subsequently causes maladaptive responses in immune function, fuel production, and synthesis of mediators that cause further tissue and organ dysfunction. Thus, the combination of hyperglycemia and relative hypoinsulinemia is mechanistically positioned to provide a plausible explanation for the poor hospital outcomes seen in observational studies (27).

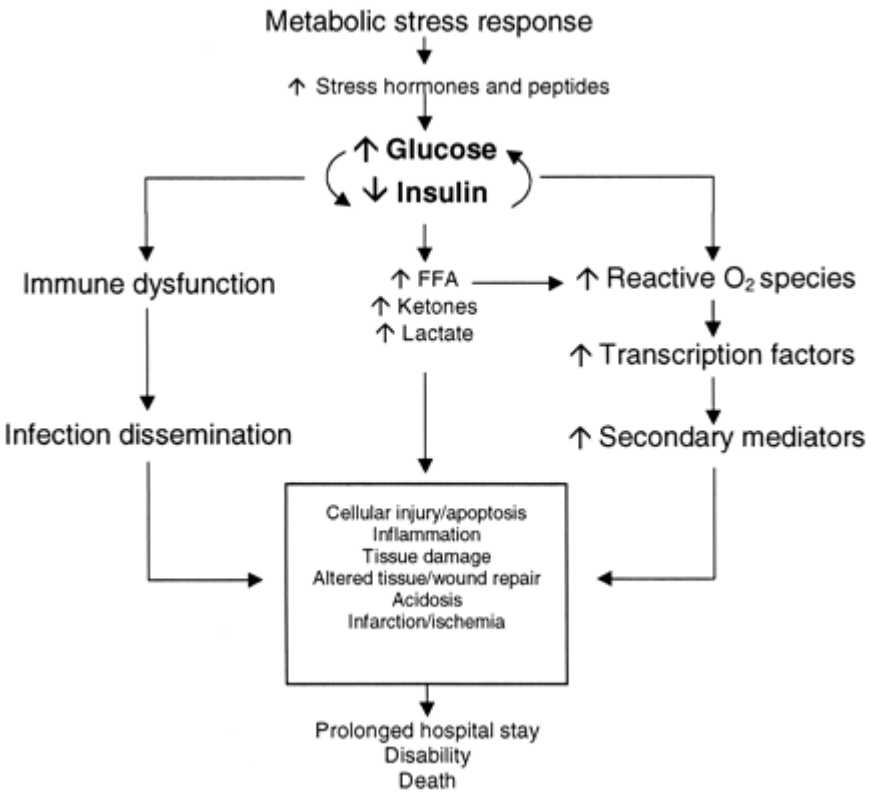


Figure 1— Link between hyperglycemia and poor hospital outcomes

Stress hyperglycemia and short and long term mortality:

The role of admission glycaemia in non diabetic patients with acute myocardial infarction, however, has been less extensively studied. Fuller JH et al. has shown his studies that people with impaired glucose tolerance have a cardiovascular mortality rate twice that of their counterparts with normal glucose tolerance (33). In most prior studies during the thrombolytic era, mortality among diabetic patients has generally been much lower, although a recent report from Sweden reported two year mortality rate of 40% in patients who represented with a known diagnosis of diabetes.

The overall mortality of patients with stress hyperglycemia as per Nordin et al. was also strikingly high as 53 %(34). This high mortality rate is not the result of low rates of either aggressive interventions or prescriptions for appropriate cardiovascular medications, at least during the hospitalization and on discharge and rather suggests that the major reason is a very advanced level of cardiovascular disease than the normal.

It has been well demonstrated that patients with admission hyperglycemia are associated with increased risk of mortality after AMI. This association has been observed not only in diabetic patients but also patients who had no previous diagnosis of diabetes (34).

Recent experimental and clinical studies suggested that rapid elevation of plasma glucose itself increases infarct size. Hyperglycemia activates blood coagulation, aggregates inflammation, attenuates endothelium function, and abolishes ischemic preconditioning (34).

Sarah E capes et al showed in their review article that patients without diabetes who have stress hyperglycemia on admission for acute myocardial infarction are at increased risk of in-hospital mortality and congestive cardiac failure. Several possible mechanisms may explain this observation (30).

First, hyperglycemia is reflection of relative insulin deficiency, which is associated with increased lipolysis and excess circulating free fatty acids; this effect may be exaggerated in cases of acute stress such as myocardial infarction. Free fatty acids, although normally the substrate of choice for healthy myocardium, are toxic to ischemic myocardium and may lead to damaged cardiac-cell membranes, calcium overload, and arrthymias (34).

Moreover, in animal studies, high concentrations of free fatty acids during myocardial infarction increase myocardial oxygen demands and reduce myocardial contractility. Beta blockers suppress the increase in free fatty acids in patients with myocardial infarction, and may lessen the harmful effects of hyperglycemia and insulin deficiency. They did not explore this hypothesis in the overview because the only study that stated that beta blockers were administered provided no information about the interaction between these drugs and stress hyperglycemia on the risk of outcomes after MI (34).

Second, acute hyperglycemia may precipitate an osmotic diuresis. The resulting volume depletion may interfere with the frank- starling mechanism, an important compensatory mechanism for the failing left ventricle in which increased end- diastolic volume leads to increased stroke volume (34).

Third, stress hyperglycemia may be marker of more extensive cardiac damage in acute myocardial infarction. More extensive cardiac damage may lead to a greater rise in stress hormones (promoting glycogenolysis and hyperglycemia) and may also increase the risk of congestive cardiac failure and mortality. Thus, stress hyperglycemia could simply be an epiphenomenon reflecting the most severe cardiac damage. However, stress hyperglycemia is an imperfect marker of the extent of cardiac damage, since many other factors in addition to stress hormones (such as insulin resistance and the capacity of the pancreas to secrete insulin) contribute to the regulation of glucose concentrations (34).

Fourth, patients who develop stress hyperglycemia are likely to be dysglycaemic when not stressed. Patients with dysglycaemia are at a higher risk of cardiovascular disease than patients who have normal glucose, and may have a worse prognosis after acute myocardial infarction because of extensive underlying coronary artery disease (34).

Stress hyperglycemia was also associated with an increased risk of mortality in the Diabetes and the effect was smaller than that in patients without diabetes. There are several possible reasons. Patients with diabetes are more likely to receive insulin for hyperglycemia during myocardial infarction and the rise in free fatty acids during MI, promote myocardial uptake of glucose for anabolic metabolism and decrease coagulablity because of reduced production of thromboxane A and PAI 1 activity (34).

The threshold values that defined hyperglycemia in the individual studies may have been too low to

distinguish between patients with diabetes who did and did not have stress hyperglycemia. More over the definition of stress hyperglycemia is intrinsically difficult in patients with baseline concentration of glucose is not known.

Kadri et al analysed the short term and long term prognostic significance of admission glycemia in 1604 non-diabetic patients with AMI (8). The conclusion were even in non- diabetic patients hyperglycemia on admission is independently associated with a higher risk of developing acute left ventricular failure as well as with a higher risk of in hospital and long term mortality

Bartnik et al assessed whether newly detected abnormal glucose tolerance early after an MI relate to long term prognosis (34). 168 patients with myocardial infarction, no diabetes and admission blood glucose < 11 mmol/L were followed for major cardio vascular events like cardio vascular death, non-fatal MI, non-fatal stroke or severe heart failure. Cardio vascular events occurred in 18% patients. He concluded that abnormal glucose tolerance is a strong risk factor for further cardio vascular events after MI. Elevated plasma glucose and glycated haemoglobin levels on admission are independent prognosticators of both in-hospital and long term outcome regardless of diabetic status. For every 18 mg/ dL increase in glucose level, there is a 4% increase in mortality in non diabetic subjects. When admission glucose level exceeds 200 mg/L mortality is similar in non DM and DM subjects with MI. Admission glucose has been identified as a major independent predictor of both in-hospital congestive heart failure and mortality in STEMI.

Stress hyperglycemia and severe coronary artery disease:

Although stress hyperglycemia is a risk factor not only for cardiovascular morbidity and mortality but

also for severe coronary artery disease. Chirstopher Nielson et al. showed in his studies that elevated glucose in the absence of diabetes is associated with greater incidence of CAD independent of other recognized risk factor including age, weight, hyperlipidemia, renal failure, and hypertension (29). Hyperglycemia promotes atherogenesis by several possible mechanisms, including increased generation of free radicals, decreased production of nitric oxide, activation of the polyol pathway and the diacylglycerol protein kinase C system and increases in nonenzymatic glycation products and the glycosylation of certain proteins (29).

Coutinho et al. has pointed out that if stress hyperglycemia indeed reflects an underlying dysglycemic state, then this would be expected to correlate with a higher overall risk for more extensive CAD and would explain a worse prognosis after AMI (35). Thus, elevated plasma glucose would both reflect the acute stress and predict an increased propensity for severe coronary artery disease. Thus data suggest that stress hyperglycemia, serves as a marker for very advanced coronary artery disease and become the dominant determinant of mortality similar to preexisting diabetes mellitus (35).

Stress hyperglycemia and Cardiac surgery.

Attainment of targeted glucose control in the setting of cardiac surgery is associated with reduced mortality and risk of deep sternal wound infections. Furnary and colleagues (46, 47) treated cardiac surgery patients with diabetes with either subcutaneous insulin (years 1987–1991) or with intravenous insulin (years 1992–2003) in the perioperative period. From 1991–1998, the target glucose range was 150 -200 mg/dl (8.3–11.1 mmol/l); in 1999 it was dropped to 125–175 mg/dl (6.9–9.7 mmol/l), and in 2001 it was again lowered to 100–150 mg/dl (5.5–8.3 mmol/l).

Following implementation of the protocol in 1991, the authors reported a decrease in blood glucose

level for the first 2 days after surgery and a concomitant decrease in the proportion of patients with deep wound infections, from 2.4% (24 of 990) to 1.5% (5 of 595) ($P < 0.02$) (47). A recent analysis or the cohort found a positive correlation between the average postoperative glucose level and mortality, with the lowest mortality in patients with average postoperative blood glucose <150 mg/dl (8.3 mmol/l) (48).

Golden et al. (49) performed a nonconcurrent prospective cohort chart review study in cardiac surgery patients with diabetes (n = 411). Perioperative glucose control was assessed by the mean of six capillary blood glucose measures performed during the first 36 h following surgery. The overall infectious complication rate was 24.3%.

After adjustment for variables, patients with higher mean capillary glucose readings were at increased risk of developing infections. Compared with subjects in the lowest quartile for blood glucose, those in quartiles 2–4 were at progressively increased risk for infection (RR 1.17, 1.86, and 1.78 for quartiles 2, 3, and 4, respectively, $P = 0.05$ for trend). These data support the concept that perioperative hyperglycemia is an independent predictor of infection in patients with diabetes.

Stress hyperglycemia and Critical care.

Van den Berghe et al. (50) performed a prospective, randomized controlled study of 1,548 adults who were admitted to a surgical intensive care unit and were receiving mechanical ventilation. Reasons for ICU admission were cardiac surgery (~60%) and noncardiac indications, including neurologic disease (cerebral trauma or brain surgery), other thoracic surgery, abdominal surgery or peritonitis, vascular surgery, multiple trauma, or burns and transplant (4–9% each group).

Patients were randomized to receive intensive insulin therapy (IIT) to maintain target blood glucose in

the 80–110 mg/dl (4.4–6.1) range or conventional therapy to maintain target blood glucose between 180 and 200 mg/dl (10–11.1 mmol/l). Insulin infusion was initiated in the conventional treatment group only if blood glucose exceeded 215 mg/dl (11.9 mmol/l), and the infusion was adjusted to maintain the blood glucose level between 180 and 200 mg/dl (10.0 and 11.1 mmol/l). After the patients left the ICU they received standard care in the hospital with target blood glucose of 180 and 200 mg/dl (10.0 and 11.1 mmol/l).

Ninety-nine percent of patients in the IIT group received insulin infusion, as compared with 39% of the patients in the conventional treatment group. In the IIT arm, blood glucose levels were 103 ± 19 mg/dl (5.7 ± 1.1 mmol/l) and in conventional treatment 153 ± 33 mg/dl (8.5 ± 1.8 mmol/l). IIT reduced mortality during ICU care from 8.0% with conventional treatment to 4.6% ($P < 0.04$). The benefit of IIT was attributable to its effect on mortality among patients who remained in the unit for more than 5 days (20.2% with conventional treatment vs. 10.6% with IIT, $P = 0.005$). IIT also reduced overall inhospital mortality by 34%. In a subsequent analysis, Van den Berghe (55) demonstrated that for each 20 mg/dl (1.1 mmol/l), glucose was elevated >100 mg/dl (5.5 mmol/l) and the risk of ICU death increased by 30% ($P < 0.0001$).

Daily insulin dose (per 10 units added) was found as a positive rather than negative risk factor, suggesting that it was not the amount of insulin that produced the observed reduction in mortality. Hospital and ICU survival were linearly associated with ICU glucose levels, with the highest survival rates occurring in patients achieving an average blood glucose <110 mg/dl (6.1 mmol). An improvement in outcomes was found in patients who had prior diabetes as well as in those who had no history of diabetes.

Evidence for a blood glucose threshold in cardiac surgery and critical care.

Furnary et al. (46) and Zerr et al. (49) identified a reduction in mortality throughout the blood glucose

spectrum with the lowest mortality in patients with blood glucose <150 mg/dl (8.3 mmol/l).
Van den Berghe et al. (50), using intensive intravenous insulin therapy, reported a 45% reduction in ICU mortality with mean blood glucose of 103 mg/dl (5.7 mmol/l), as compared with the conventional treatment arm, where mean blood glucose was 153 mg/dl (8.5 mmol/l) in a mixed group of patients with and without diabetes.

Stress hyperglycemia and therapeutic prospects:

Early diagnosis of hyperglycemia in MI patients provides an opportunity for appropriate intensive management. More recently, it has been shown that the treatment of these conditions with intravenous infusions of insulin results in marked improvements in clinical outcomes. The concept of a metabolic cocktail to stabilize cell membranes through potassium influx, promote glucose oxidation, and reduce free fatty acid accumulation to protect the ischemic myocardium dates back to the work of Sodi – pallares et al (36).

Is insulin anti-inflammatory (17)?

Mortality and infarct size in AMI may be reduced by therapies influencing myocardial metabolism, such as infusion of glucose-insulin potassium. It is proposed that the balance between insulin and plasma glucose levels is critical to recovery and or complications that occur following AMI and critical illness.

Early studies (DIGAMI) yielded promising results, and a meta- analysis suggested that therapy with GIK may reduce mortality in STEMI. However, the clinical trial of metabolic modulation in acute

myocardial infarction treatment evaluation- Estudios cardiologicos Latino America(CREATE-ECLA) study showed no benefit of GIK in a large number of STEMI subjects, dampening the enthusiasm for aggressive use of a metabolic cocktail in STEMI(8).

But recently published study by C Weston et al showed that in non-diabetic patients with acute coronary syndrome and hyperglycemia, treatment with insulin was associated with a reduction in the relative risk of death, evident within seven days of admission, which persists at 30 days (11).

However it is necessary to distinguish between a favorable metabolic effect of glucose-insulin infusion and the control of acute hyperglycemia. In terms of metabolic efficacy it has been suggested that insulin, by itself, should have direct beneficial effect, particularly in reducing the level of free fatty acids, which are known to be associated with a deterioration of clinical outcome and may have toxic effects of their own on the myocardium.

On closer examination, it is clear that not all studies were comparable to each other because the concentrations of glucose and insulin used in those studies were not uniform. Studies in which higher concentrations of insulin were used showed better results than did those studies that employed a lesser dose.

On the basis of the above discussion, it should be clear that any elevations of plasma glucose are likely to be pro inflammatory and thus potentially harmful. Even mild hyperglycemia is associated with poor outcome after AMI. It is generally believed that the GIK regimen improves the integrity and function of myocardial cell once glucose and potassium are transported in by insulin. The administration of insulin is likely to be anti- inflammatory and thus may be clinically beneficial.

Therefore, the true open question is whether hyperglycemia, when present during a MI, has to be treated with intensive insulin therapy even in non-diabetic patients. While waiting for specific trials, it should be helpful to consider that intensive insulin therapy has already shown a beneficial effect in critically ill patients (17). .

This early, simple, and inexpensive marker of bad prognosis after MI should prompt the application of more aggressive treatment of MI and modification of risk factors including of glycaemia during admission (17).

Methods

Study design and patients

We enrolled patients from among those who presented with acute myocardial infarction and were admitted in the coronary care unit of our hospital Christian medical college, Vellore, India between Jan 2006 to Dec 2007. These were patients who survived the acute event and agreed for a coronary angiogram (CAG) or underwent CAG during a primary angioplasty for the acute event.

A total of 144 patients both diabetic and non diabetic were studied. Of these, 61 patients were being treated for diabetes. The remaining 83 patients were classified depending on the results of a 75 gm oral glucose tolerance test before discharge into normal glucose tolerance (NGT)(n=36) and stress hyperglycemia (n=47). All patients in the non diabetic group had HbA1c below 6.5% at the time of admission and also their glucose levels were within normal range at the end of one month.

We did not recruit individuals who had serum creatinine concentrations more than 2mg% or age more than 70 years. All the patients were treated as per established Additional revascularization procedures were performed for symptoms or signs of myocardial ischemia. The medications were given as per ACC/ AHA guidelines.

We defined acute myocardial infarction according to the criteria jointly recommended by the European society of cardiology and the American college of cardiology (7). Thus, patients were diagnosed as having an acute myocardial infarction if they had two values of serum troponin I greater than 0.2 g/L or CK-MB greater than 20 ug/L with either typical symptoms (chest pain more than 20 min: pulmonary

edema in the absence of valvular heart disease: cardiogenic shock: arrhythmias such as ventricular fibrillation or ventricular tachycardia) or new Q waves in at least two of the twelve standard electrocardiographic leads, or electrocardiogram changes indicating acute ischemia (ST elevation, ST-depression, or T wave inversion.)

Data collection: Patients cardio vascular history, their medications at the time of admission, their risk factors, in hospital clinical course, including Killips class, the initial diagnostic and therapeutic management were recorded Furthermore, left ventricular ejection fraction, assessed at any time during the first five days, was recorded.

Assessment of traditional risk factors

Glucose tolerance test

A total of 144 patients were studied. Of these, 61 patients were being treated for diabetes mellitus. In all patients except those with diabetics an oral glucose tolerance test (glucose load of 75 g) was performed between 8:00 and 10:00 a.m. after 8 hours fasting within 5 days of the admission. Blood was sampled before, and 2 h after the glucose loading and the plasma glucose concentration was determined by the glucose oxidase method. The results of the test were analyzed according to the World Health Organization criteria and the patients were classified into three groups; normal glucose tolerance, defined as a fasting plasma glucose concentration <110 mg/dl and a 2-h plasma glucose concentration <140 mg/dl; stress hyperglycemia, defined as a fasting plasma glucose >110 mg % and a 2-h plasma glucose concentration > 140mg% and the patients with DM. All the patients in the stress hyperglycemia

group had normal plasma glucose value at one month of follow up and it indicates hyperglycemia only secondary to stress of myocardial infarction.

Systemic hypertension

Systemic hypertension was considered to be present if the patients had been taking antihypertensive drugs or if their systolic blood pressure was ≥140 mmHg or the diastolic blood pressure was ≥90 mmHg on two measurements of their blood pressure during hospitalization.

Evaluation of smoking

The amount of smoking expressed as smoking index was calculated by the number of cigarettes smoked daily multiplied by the number of years the patient had been smoking.

Measurement of serum lipids

Blood was sampled after 8 hours fasting on the second hospital day. Serum concentrations of total cholesterol, triglyceride (TG), and high-density lipoprotein cholesterol (HDLc) and low-density lipoprotein cholesterol (LDLc) were determined enzymatically.

Evaluation of the severity of coronary atherosclerosis.

Selective coronary angiography was performed in multiple projections. Analyses of coronary angiogram were performed by independent cardiologists. Presence of minor coronary artery disease was defined if the internal luminal diameter narrowing was less than 50% .Internal luminal diameter narrowing more than 50% was considered significant coronary artery disease. The percent diameter stenosis was obtained by comparing the diameter of an obstructed segment with the nearest normal vessel diameter on a projection view that showed the obstruction in its maximum severity (8). Based on the coronary angiography, to classify the extent of coronary artery disease, patients were divided into three categories:

Category1. Normal or minor coronary artery disease (< 50%stenosis)

Category2. Significant single coronary artery disease (>50%stenosis)

Category3. Multi vessel coronary artery disease (significant stenosis >50% in more than one vessel)

Statistical analyses

To evaluate the relation ship of stress hyperglycemia with multi vessel disease, statistical analyses were performed using SPSS 11. A p value < 0.01 was considered statistically significant.

Data for both continuous and categorical variables were presented as proportions and counted in terms of absolute and relative frequency distributions.

Both continuous and discrete variables were compared with Chi-square test.

Multiple logistic regression analysis was performed to assess independent predictors of multi vessel disease after adjusting for baseline characteristics and variables.

Baseline characteristics:

Pertinent clinical characteristics of three groups of the patients (NGT, SH, DM) as seen during hospital phase, are presented in Table 1.

Table 1 Baseline characteristics:

Variables	NGT(n)	SH(n)	DM(n)	P value
Age >55	30	28	30	.004
Male sex	33	39	49	.329
Hypertensive	13	18	34	.089
smokers	18	12	14	.044
HDL <40	31	41	49	.577
LDL>130	30	27	38	.035
TGL>160	32	38	48	.439
Anterior wall MI	25	32	48	.506
Inferior wall MI	3	3	1	
Complicated inferior wall MI	8	12	12	

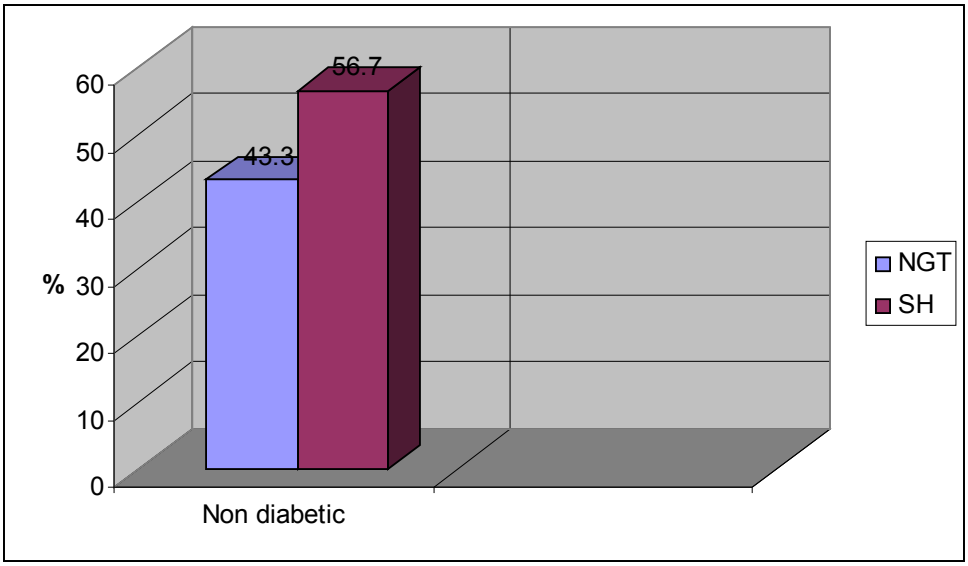
There was no significant difference among the patients in the three groups as regards the variables.

Prevalence of Stress hyperglycemia in non diabetics

A total of 144 patients both diabetic and non diabetic were studied. Of these, 61 patients were being treated for diabetes. The remaining 83 patients were classified depending on the results of a 75 gm oral glucose tolerance test which was done before discharge into normal glucose tolerance 43.3% (n=36) and stress hyperglycemia 56.7% (n=47) fig(2). All the non-patients who had high plasma glucose sugar (Stress Hyperglycemia) following acute myocardial infarction had normal plasma glucose levels when checked after one month. The prevalence of stress hyperglycemia in the absence of a history of diabetes was 56.7% and appears to be similar to that seen in other patient populations.

Figure 1. Bar chart showing the prevalence of stress hyperglycemia

in non diabetic MI patients



Comparison of NGT, SH, DM in patients with anterior wall, inferior wall,

and complicated inferior wall MI.

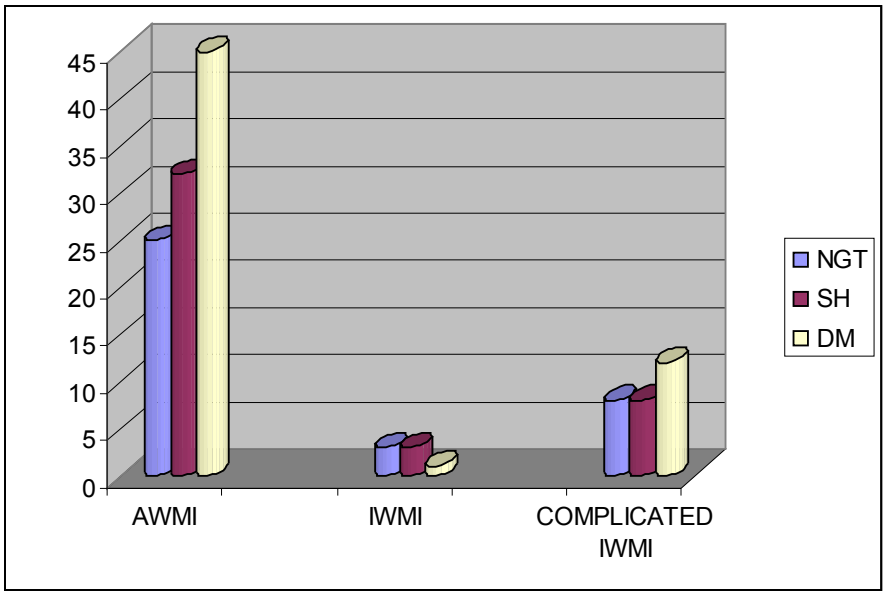
NGT, SH, DM was noticed 23.8%, 30.5%, and 45.7% respectively in patients with anterior wall myocardial infarction. Similarly, 42.9%, 42.9%, 14.3% in inferior wall myocardial infarction patients and 25%, 32.6%, and 37.5% in patients with complicated inferior wall myocardial (table2, fig 2).

Table 2. showing the comparison of NGT, SH, DM in patients with anterior

wall, inferior wall, and complicated inferior wall MI.

	Glucose tolerance			Total(n)
	NGT(n)	SH(n)	DM(n)	
AWMI	25	32	48	118
IWMI	3	3	1	26
Complicated IWMI	8	12	12	32
Total	36	47	61	144

Figure 2. Bar chart showing the comparison of NGT, SH, DM in patients with anterior wall, inferior wall, and complicated inferior wall MI.



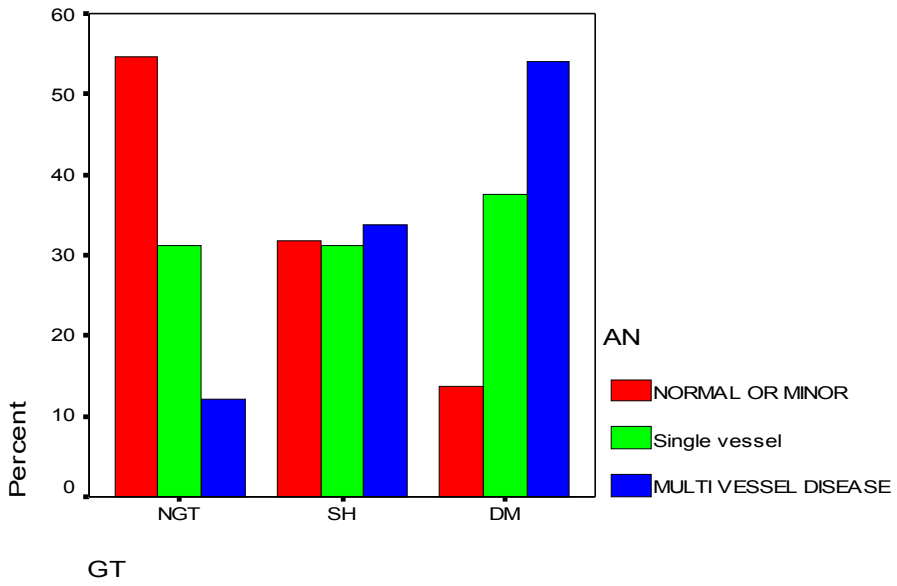
Association between the glucose metabolism and coronary atherosclerosis:

In our study, 33.8% patients with stress hyperglycemia (n=25), 54.1% diabetic patients (n=40), and 12.2% patients with normal glucose tolerance (n=9) had multi vessel disease with significant P value of <.001(table3 and Fig 3). These results indicate that prevalence of multi vessel disease in stress hyperglycemia was similar to that in diabetic patient but differ from that in patients with normal glucose tolerance.

Table 3: showing the angiographic profile among NGT, SH, DM

	Glucose tolerance			Total(n)	P value
	NGT(n)	SH(n)	DM(n)		
Normal or minor	12	7	3	22	<.001
Single vessel	15	15	18	48	
Multi vessel	9	25	40	74	
Total	36	47	61	144	

Figure 3: Bar chart showing the angiographic profile among NGT, SH, DM



Multivariate analysis

We performed univariate and multivariate analyses to investigate which of the clinical variables and risk factors were independently associated with multivessel disease in acute MI.. Age, male sex, LDL level, stress hyperglycemia, anterior wall myocardial infarction and inferior wall infarction were significant predictors of multivessel disease by univariate analysis. By multivariate analysis, age, male sex and stress hyperglycemia were independent predictors. Among these parameters, stress hyperglycemia was shown to be independently and significantly associated with multivessel disease (odds ratio 4.6, 95 % confidence interval 1.17 to 18.7) with significant P value of 0.028.

Table 4: Multivariate analysis shows stress hyperglycemia is independent predictor of multivessl disease

variables	Odds ratio		95% confidence interval		P value
	Multivessel disease	Single vessel disease	Multivessel disease	Single vessel disease	
Age >55	3.376	1.921	.869	13.109	.079
Male sex	6.223	6.282	1.488	26.027	.012
LDL>130	1.982	.991	.272	3.612	.989
Stress hyperglycemia	4.6	2.1	1.177	18.752	.028
AWMI	.298	2.1	6.7E	1.3	.110
IWMI	.189	1.117	.308	7.567	.186

Discussion

Diabetes mellitus is an established major cardiovascular risk factor associated with increased prevalence of coronary artery disease. Patients with diabetes mellitus often have numerous concomitant cardiac risk factors with a higher incidence of acute myocardial infarction and congestive heart failure (CHF) (1). Interestingly, this increased risk is not confined to the patients with DM, but non diabetic patients with impaired glucose tolerance also may have an increased incidence of cardiovascular complications. Consequently, hyperglycemia at the time of myocardial infarction in patients with and without diabetes may be an important and potentially modifiable risk factor for poor outcome (1).

To our knowledge, our series was the first to date describing the impact of stress hyperglycemia on the severity of the coronary artery disease in non diabetic patients with acute myocardial infarction. The main purpose of this study is to describe the relationship between stress hyperglycemia and severity of coronary artery disease in non diabetic patients.

The present study not only confirms the increased prevalence of stress hyperglycemia after acute myocardial infarction, but further corroborates the significance of this variable as a predictor of severe coronary artery disease in diabetic and non diabetic subjects.

Prevalence and risk of hyperglycemia in STEMI:

The prevalence of stress hyperglycemia with myocardial infarction is not known. Stress hyperglycemia is common in patients with AMI. Two thirds of patients with acute myocardial infarction who had no previous diagnosis of diabetes had abnormal glucose tolerance as tested by oral glucose tolerance test

immediately after acute myocardial infarction. These abnormalities can be detected early in the post infarction period.

An unusually high prevalence of glucosuria in patients without diabetes who have AMI was noted as far back as 1931. Wahlberg in 1966 reported that patients with an AMI may present with elevated blood glucose (5).

Acute hyperglycemia is common in patients with ST elevation myocardial infarction (STEMI) even in the absence of a history of type 2 DM (4). Hyperglycemia is encountered in up to 50% of all STEMI patients, whereas previously diagnosed DM is present in only 20-25% STEMI patients (37). The prevalence of stress hyperglycemia in patients with out diabetes ranged from 5% to 71% and the overall pooled prevalence was 13.7% of the total number of the patients with myocardial infarction (2)

The prevalence of hyperglycemia in non diabetic subjects with acute coronary syndrome in Indian patients was 59 %(38). Post glucose hyperglycemia was also found in Japanese patients presented with ACS who were not found previously diagnosed to have diabetes with a prevalence of 47% (38).

In another study, oral glucose tolerance test in non diabetic patients with acute myocardial infarction at hospital discharge was done and 66% of the patients were diagnosed to have stress hyperglycemia (39). Recently, the Euro Heart Survey on diabetes and the heart reported that oral glucose tolerance test identified 58% of the 923 non diabetic patients with acute coronary syndrome as having SH (40).

These findings are consistent with our study. In our study the prevalence of stress hyperglycemia in the absence of a history of diabetes was 57.8% and appears to be similar to that seen in other patient populations. Supporting the biologic reality of this diagnostic category is the high overall mortality in this group, which is similar to the patients with myocardial infarction and diabetes. These results show that prevalence of stress hyperglycemia is strikingly high in our population.

Stress hyperglycemia is an independent predictor of severe coronary artery disease

Among patients with no prior history of diabetes, stress hyperglycemia may reflect previously undiagnosed diabetes, pre existing carbohydrate intolerance, stress related carbohydrate intolerance, or a combination of these(2). Studies have reported an association between elevated blood glucose at hospital admission and subsequent increased adverse events including CHF, cardiogenic shock, and death (10, 21, 34, and 35). Therefore, we investigated the possible association of stress hyperglycemia in patients with acute myocardial infarction, with the presence of multivessel disease in non diabetic patients. These patients plasma glucose level revered to normal after one month.

The main finding of the study was that abnormal glucose tolerance, identified before hospital discharge of patients with AMI, characterized individual with high likelihood for severe coronary artery disease. Together with acute myocardial infarction, the glucometabolic state is the strongest predictor of future cardiovascular events.

Previous studies have demonstrated that patients with AMI and stress hyperglycemia are at increased risk of mortality and congestive heart failure (2, 15, 29, and 33).

Moreover, it has been suggested that stress hyperglycemia associated risk may be greater in patients with myocardial infarction who do not have antecedent diabetes than in those with diabetes and this mortality was not limited to the early in hospital phase but extended up to one year of follow-up(21).

Although there is a large consensus regarding the prognostic impact of stress hyperglycemia both short and long term after MI in non diabetic patients, the exact mechanism underlying this association remain poorly understood.

Several studies have suggested that plasma glucose levels at hospital admission may be associated with larger infarct size (42), worse LV function (43). Some previous studies have suggested that stress hyperglycemia could reduce collateral flow to the risk area and could abolish the effect of preconditioning (44), or may be associated with the no reflow phenomenon (44). But these observations are still to be proven conclusively.

DM is one of the major cardiovascular risk factors and stress hyperglycemia is increasingly recognized as a cardiovascular risk factors. However, the association of stress hyperglycemia with the severity of coronary artery disease is not fully understood

A recently published one study showed that the prevalence of stress hyperglycemia was significantly greater in patients with multi-vessel disease than in those with zero-vessel disease (42). In another study, there was no significant difference in the severity of angiographic coronary atherosclerosis between patients with NGT, IGT, and DM (45)

These studies however did not include patients with AMI and had small number of subjects and

represented the severity of coronary atherosclerosis by the mean degree of coronary stenosis.

In our study, 53.2% patients with stress hyperglycemia, 65.2% patients with diabetes mellitus and 33,2% patients with normal glucose tolerance had multi vessel disease with significant P value of <0.001. By multivariate analysis, stress hyperglycemia was shown to be independently associated with multi vessel disease.

Our results suggest that there is a strong correlation between stress hyperglycemia and severe coronary artery disease. Hence stress hyperglycemia in early phase of an acute myocardial infarction could be used as early marker for risk stratification.

Clinical implications:

Patients with stress hyperglycemia on admission may represent individuals who do not meet the diagnostic criteria of diabetes mellitus but have a mild form of impairment in glucose metabolism, and may develop hyperglycemia during stressful conditions, such as AMI.

This sub diabetic is also known as stress hyperglycemia (42). As these patients also appear to have an increased mortality rate after acute myocardial infarction, specific risk reducing interventions for these

patients are to be considered.

To our knowledge, our series is the first till date describing the association of stress hyperglycemia with the severity of coronary artery disease in non diabetic patients with AMI. It documents that the association between increased blood glucose concentrations and outcomes is not confined to the patients with diabetes but also to stress hyperglycemia which is potent predictor of severe coronary artery disease.

Identifying patients prone for severe coronary artery disease who are at risk for sustaining adverse cardio vascular events is an integral part of management after AMI. High risk patients could indeed be stratified for more aggressive therapy and for more intensive follow up.

Although various predictive factors of severe coronary artery disease have been suggested by prior studies, there is still a need for non invasive, widely available, and relatively inexpensive methods to estimate the risk of severe coronary artery after AMI in routine clinical practice.

At present, risk stratification is largely based on the results of pre discharge treadmill. If confirmed in independent studies, our finding that stress hyperglycemia is a strong independent predictor of severe coronary artery disease, may have important clinical implication.

Recently, another study also showed that abnormal glucose tolerance is a strong risk factor for future cardiovascular events after acute myocardial infarction. The difference in the incidence of cardiovascular events between patients with diabetes and the patients with IGT was negligible (40). Taking this into account, oral glucose tolerance test could be routinely considered for the risk

stratification.

These abnormalities can be detected early in the post infarction period by quick, inexpensive tests such as oral glucose tolerance test, which are seldom done in coronary care units. These findings underline the need for aggressive glucose management in this setting and may support a more vigorous strategy for early recognition of stress hyperglycemia. Hence oral glucose tolerance test should be considered in all non- diabetic patients with acute myocardial infarction.

These findings warrant further investigation regarding glycometabolic control during AMI and aggressive application of established secondary prevention strategies including lipid lowering therapy, anti platelet therapy, and treatment of hypertension in patients with stress hyperglycemia.

Exercise training, dietary modification, and medical intervention reduce the risk of subsequent DM in these patients and may be of value. However, intervention during hospitalization also may also be of benefit.

Interestingly, intensive insulin regimen in patients with DM with AMI abolished the increase in mortality rates associated with stress hyperglycemia. Whether insulin therapy or intervention through other hypoglycemic agents is also beneficial for the patients with stress hyperglycemia with AMI is unknown. In non diabetic patients with acute coronary syndrome and hyperglycemia, treatment with insulin was associated with a reduction in the relative risk of death, evident within 7 days of admission, which persists at 30 days (11).

Future studies should assess whether more aggressive glucometabolic therapies should be added to

these established intervention for the patients with stress hyperglycemia. Resolving the issue would be of interest from both clinical and an experimental point of view.

Previous studies have shown that stress hyperglycemia is associated with increased short and long term mortality. Our findings suggest that stress hyperglycemia in addition is also associated with severe coronary artery disease.

Above findings suggest that adequate metabolic control of blood glucose would be an important treatment target, even in non diabetic patients, to limit the deleterious effect of increased blood glucose in the setting of acute myocardial infarction, the best therapeutic methods to achieve such a goal, however, remain to be determined.

Study limitations:

We were aware of certain limitations: This study is observational, prospective and non- randomized and included only a limited number of patients from a single center. The majority of patients were men, so the degree to which the conclusion applies to women is unclear. However, it does reflect the real world population in that it includes all consecutive patients hospitalized with AMI.

Despite these limitations, the results of our study may contribute to characterize the prognosis of patients with stress hyperglycemia in patients presenting with acute myocardial infarction.

Conclusion:

The present study provides further evidence to support the previous finding that stress hyperglycemia is common in AMI in non diabetic patients

This study also suggests that the severe coronary artery disease is present not only in the diabetes groups but also in the stress hyperglycemia group.

Our study demonstrates an additional aspect of how stress hyperglycemia contributes to poor outcome in MI patients with or without diabetes.

Stress hyperglycemia is an early simple and inexpensive marker of severe coronary artery disease in patients with AMI. Hence an oral glucose tolerance test can easily be added to the standard risk evaluation procedures in patients with acute myocardial infarction and may be of value for enhanced secondary prevention.

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GLOSSARY FOR THE MASTER SHEET

DM - Diabetes mellitus.

AMI - Acute myocardial infarction.

SH - Stress hyperglycemia

CAD - Coronary artery disease

CAG - Coronary angiogram

NGT - Normal Glucose tolerance

TG	-	Triglycerides
HDL	-	High density cholesterol
LDL	-	Low density cholesterol
HbA1c	-	Glycosylated haemoglobin A1c
OGTT	-	Oral glucose tolerance test
PG	-	Plasma glucose
STEMI	-	ST elevation myocardial infarction
PAI	-	Plasminogen activator inhibitor 1 activity
IL	-	Interleukin
PCI	-	Percutaneous coronary intervention
IIT	-	Intensive insulin therapy
CHF	-	Congestive heart failure.
ACS	-	Acute coronary syndrome